Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis — A Comprehensive Review and Guide to Therapy. I. Systemic Disease

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ABSTRACT **The intent of this review is to comprehensively appraise the state of the art with regard to Stevens Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with particular attention to the ocular surface complications and their management. SJS and TEN represent two ends of a spectrum of immune-mediated, dermatobullous disease, characterized in the acute phase by a febrile illness followed by skin and mucous membrane necrosis and detachment. The widespread keratinocyte death seen in SJS/TEN is rapid and irreversible, and even with early and aggressive intervention, morbidity is severe and mortality not uncommon. We have divided this review into two parts. Part I summarizes the epidemiology and immunopathogenesis of SJS/TEN and discusses systemic therapy and its possible benefits. We hope this review will help the ophthalmologist better understand the mechanisms of disease in SJS/TEN and enhance their care of patients with this complex and often debilitating disease. Part II (April 2016 issue) will focus on ophthalmic manifestations.**

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OUTLINE

KEY WORDS apoptosis, drug-induced disease, immune-mediated disease, keratinocyte death Stevens-Johnson Syndrome, toxic epidermal necrolysis

I. INTRODUCTION

The spectrum of disease defined by Stevens-Johnson Syndrome (**SJS**), the more severe toxic epidermal necrolysis (**TEN**), and their intermediate (SJS/TEN overlap) characterize a severe immunologic dermatobullous condition with high mortality and significant long-term morbidity. SJS/TEN is characterized by widespread keratinocyte death and epidermal necrosis resulting in splitting of subepidermal layers with attendant tissue loss at skin and mucosal surfaces.[1] The diagnosis of SJS/TEN is made upon recognition of defining clinical signs and skin biopsy demonstrating full-thickness necrosis of the epidermis and keratinocyte apoptosis, with minimal involvement of the underlying dermis.[2-5]

The purpose of Part I of this review is to summarize the most up-to-date information on SJS/TEN, with particular attention to pathogenesis and systemic therapy. SJS/TEN is a rare disease, and there is a paucity of centralized information on best care practices. This comprehensive review critically evaluates contemporary concepts of pathophysiology and the therapies currently in use for patients with the disorder. However, the authors wish to emphasize that the pathophysiology of SJS/TEN is still a matter of debate, and the best systemic therapy for SJS/TEN beyond general supportive burn care remains highly controversial among burn center physicians, often even within the same burn center. The ophthalmic manifestations of SJS/TEN and their management will be covered in Part II.

To provide a comprehensive, in-depth, and authoritative review of this complex entity, we assembled a group of authors who are leaders in their respective fields with experience and publications in very specific areas addressed by the review. All authors made substantial contributions in writing and revising the manuscript in their areas of expertise. Each author met Harvard Medical School criteria for authorship on a scholarly paper.

II. EPIDEMIOLOGY

A. Incidence

The estimated annual incidence (cases/million population/year) of SJS/TEN ranges from 0.4 to 7 cases per million population,[6-8] making it a rare disease.[9] There are suggestions that the incidence in certain areas of the world may be higher. In a retrospective study of 404 hospitalized patients in South India with acute cutaneous drug reactions over a 9-year period, 19.5% were diagnosed with SJS/TEN, somewhat higher than reported in other countries.[10] SJS/TEN carries a significant risk of mortality, ranging from 1-5% in SJS and 25-40% in TEN.[7,11-15] Unfortunately, despite continued efforts, mortality rates remain significant.[4] SJS predominantly affects children and adolescents, whereas TEN occurs in all ages, from premature infants to the elderly.[4] The incidence of cutaneous drug reactions including TEN is 2.7 times higher in the elderly than in younger patients, and mortality from TEN is twice as high in the elderly (51% vs 25%). However, SJS/TEN is more likely recurrent in children. In one series, 18% of 55 children developed recurrent SJS up to 7 years after the index episode, with three children experiencing more than one recurrence.[16]

B. Risk Factors

1. Non-Pharmaceutical Triggers

While SJS/TEN most often represents an idiosyncratic reaction to systemic medications, there are uncommon exceptions and the disorder can be idiopathic.[17,18] SJS/TEN has been associated with vaccination[19-21] and exposure to industrial chemicals and fumes.[19,22,23] TEN has also occurred in patients consuming natural remedies and traditional Chinese herbal medications.[24-27] Infection with *Mycoplasma pneumoniae* is a controversial cause of SJS, because *Mycoplasma* has also been associated with erythema multiforme and, in addition, can cause a primary mucositis.[28-35] Herpes virus infections have been associated with SJS,[36,37] and reactivation of herpes simplex virus has been associated with SJS recurrences, particularly in children.[16,38] Two cases of TEN have been reported in which the skin manifestations occurred specifically